REMARKS/ARGUMENTS

The Pending Claims

Claims 35, 39-42, 45-48, and 52-53 are pending and are directed to a method of changing the sensory perception of an animal.

The Amendments to the Claims

Claim 35 has been amended to specify that the pharmaceutical composition comprises an Ad28 vector. Support for this amendment can be found in the specification as filed. Specifically, paragraph 0024 teaches:

> an adenovirus can be of subgroup A (e.g., serotypes 12, 18, and 31), subgroup B (e.g., serotypes 3, 7, 11, 14, 16, 21, 34, 35, and 50), subgroup C (e.g., serotypes 1, 2, 5, and 6), subgroup D (e.g., serotypes 8, 9, 10, 13, 15, 17, 19, 20, 22-30, 32, 33, 36-39, and 42-48), subgroup E (e.g., serotype 4), subgroup F (e.g., serotypes 40 and 41), an unclassified serogroup (e.g., serotypes 49 and 51), or any other adenoviral serotype. Adenoviral serotypes 1 through 51 are available from the American Type Culture Collection (ATCC, Manassas, Va.).

Claims 50 and 51 have been cancelled. No new matter has been added by way of these amendments.

Correction and Retraction of Prior Arguments

In the replies to Office Action dated February 26, 2009, March 30, 2009, and December 17, 2009, Applicants made the following statements with respect to the Zoghbi et al. reference (U.S. Patent 6,838,444) cited in the rejections under 35 U.S.C. §§ 102 and 103.

February 26, 2009

"Moreover, the Zoghbi reference does not disclose or suggest the use of an adenoviral vector ... operably linked to a promoter that functions in supporting cells of the inner ear."

"Neither the Zine reference nor the Zoghbi patent, however, discloses or suggests employing promoters which function in supporting cells of the inner ear to control gene expression of the Hath1 gene in an adenoviral vector."

March 30, 2009

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December 17, 2009

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"Neither the Zine reference nor the Zoghbi patent, however discloses or suggests employing promoters which function in supporting cells of the inner ear to control gene expression of the Hath1 gene in an adenoviral vector."

At the time these statements were made, Applicants had a good faith belief that they were factually correct, that is, that Zoghbi et al. did not disclose a promoter that would function in supporting cells for expression of a target gene in an adenoviral vector. Upon further research and investigation, however, Applicants have determined that the above statements, while made without any deceptive intent, were factually incorrect. **Applicants, therefore, withdraw the above statements in their entirety and are no longer relying on the assertions contained therein to overcome the outstanding rejections under section 103 or for any other purpose.** Applicants further request that the Examiner disregard the foregoing statements in his consideration of the patentability of the claimed invention.

Zoghbi et al. teaches, *inter alia*, that an example of a vector falling within the scope of the invention for treating hearing or imbalance disorders is an adenovirus vector comprising a cytomegalovirus promoter sequence (see, e.g., col. 5, lines 22-23). The use of a CMV promoter in an adenoviral vector is also taught at columns 16, 34, and 48.

A further review of the state of the art, conducted subsequent to the filing of the "Reply to Office Action" dated December 17, 2009, identified several literature references teaching that an adenoviral vector (as well as an adeno-associated viral vector) comprising

the CMV promoter can drive transgene expression in supporting cells of the inner ear. Indeed, Luebke et al. (2009), Staecker et al. (2001), Ilzuka et al. (2008), and Konishi et al. (2008), identified in the Information Disclosure Statement filed herewith, confirm that the CMV promoter functions in supporting cells of the inner ear to control expression of a transgene delivered via an adenoviral vector (or via an adeno-associated viral vector). Thus, in contrast to Applicants' earlier statements, Zoghbi et al. does expressly disclose an example of a promoter that would function in supporting cells of the inner ear to control gene expression of Hath1.

Discussion of Obviousness Rejection

Claims 35, 39, 40, 41, 42, 45-48, and 50-53 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent 6,838,444 (Zoghbi et al.) and U.S. Patent 5,837,511 (Falck-Pedersen et al.) alone, or in view of (a) U.S. Patent 6,821,775 (Kovesdi et al.), (b) Staecker et al., *Otolaryngol. Head Neck Surg.*, *119*(1): 7-13 (1998), (c) U.S. Patent 6,455,314 (Wickham et al.), and/or (d) Mizuguchi et al., *Gene Ther.*, *9*(12):769-776 (2002). The substance of the rejection is set forth in the Office Action and is not repeated herein.

For subject matter defined by a claim to be considered obvious, the Office must demonstrate that the differences between the claimed subject matter and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a); see also *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). The ultimate determination of whether an invention is or is not obvious is based on the following factual inquiries: (1) the scope and content of the prior art, (2) the level of ordinary skill in the prior art, (3) the differences between the claimed invention and the prior art, and (4) objective evidence of nonobviousness. *Graham*, 383 U.S. at 17-18, 148 U.S.P.Q. at 467.

Regarding the scope and content of the prior art, Zoghbi et al. teaches a method of generating hair cells in a mammal using the genus of adenoviral vectors to deliver an atonal-associated nucleic acid. The Falck-Pedersen patent discloses methods for generating replication-deficient non-group C adenoviral vectors (i.e., subgroups A, B, D, E, and F). The

Kovesdi patent discloses an E1/E3/E4-deficient serotype 5 adenoviral vector encoding a pigment epithelium-derived factor (PEDF). The Staecker reference discloses a method of transfecting auditory hair cells with an HSV vector encoding brain-derived neurotrophic factor. The Wickham patent discloses recombinant adenovirus fiber proteins that are modified to reduce affinity for the CAR cellular receptor. The Mizuguchi reference discloses adenoviral vectors that are ablated for binding to CAR and αv-integrin, as well as adenoviral vectors containing the RGD peptide inserted into the HI loop of the fiber knob.

For the sake of argument and for purposes of the present analysis, one of ordinary skill in the art can be assumed to be someone with an advanced degree in a relevant field and a few years of experience in the relevant art.

The method defined by the pending claims comprises administering to the inner ear a serotype 28 adenoviral vector (Ad28) comprising a nucleic acid sequence encoding Hath1 operably linked to a promoter that functions in supporting cells of the inner ear, such that the nucleic acid sequence is expressed to produce Hath1 resulting in generation of sensory hair cells that allow perception of stimuli in the inner ear.

Zoghbi et al. does not explicitly teach a method of changing sensory perception in an animal by administering the specifically selected adenoviral vector recited in the amended claims, namely an Ad28 vector comprising Hath1.

Furthermore, one of ordinary skill in the art would not have had a credible reason to specifically select Ad28 from among the 51 adenoviral serotypes known in the art for use in the context of a method such as described by Zoghbi et al. with a reasonable expectation of success (see, e.g., Dharmapuri et al., *Expert Opin. Biol. Ther.*, 9: 1279-1287 (2009)). As such, the present invention – as defined by the pending claims – does not represent a "predictable solution" to the problem of improving the sensory perception of an animal.

Indeed, as demonstrated in the Rule 132 Declaration filed on December 17, 2009, the present invention as defined by the pending claims involves surprising and unexpected results. Specifically, the Rule 132 Declaration demonstrates that administration of an Ad28 vector encoding an atonal-associated gene operably linked to a promoter that functions in supporting cells of the inner ear improves vestibular function to an extent that would not have

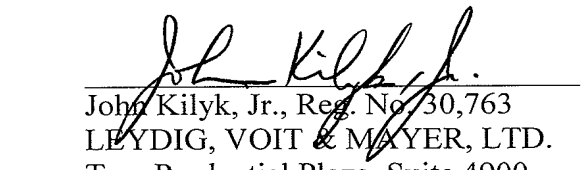
been expected and would not have been predicted by one of ordinary skill in the art in view of the cited references. Thus, the specific selection of Ad28 from among the genus of adenoviral vectors known in the art would not have been obvious because one of ordinary skill in the art would not have been able to reasonably predict the efficacy of the now claimed method based on the teachings of the prior art, whether considered alone or in combination.

Considering all of the Graham factors together, particularly the fact that the claimed invention involves surprising and unexpected results, it is clear that the present invention would not have been obvious to one of ordinary skill in the art at the relevant time in view of the combination of cited references. Accordingly, the obviousness rejections under Section 103 should be withdrawn.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned agent.

Respectfully submitted,



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